What you need to know when you prescribe a proton pump inhibitor

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Abstract
Ever since they were launched, proton pump inhibitors (PPIs) have been regarded as profligate prescription interventions and have become a favourite target for pharmacy advisers. Now that they are cheap, with generic omeprazole 20 mg daily costing £1.88 per month (£24.51 per annum) in the UK, it is time to ask whether this status should be reviewed, whether there are areas where the message should be reversed and whether there are any circumstances in which the extra cost of branded PPIs or combined preparations is justified. Equally, with the recognition of an extended toxicity profile, is prescribing profligacy not an economic but a safety issue?

Pharmacology and chemistry

PPIs are easily protonated and therefore unstable at acid pH.[1 2] In gastric juice, this would result in inactivation before absorption. This is why PPIs are enteric coated. Following absorption, they partition by ionic trapping into the acidic environment of the parietal cell cytoplasm, where the unstable sulphonamide/sulphenic acid species that result from protonation form irreversible disulphide bonds with cysteine residues in the proton pump. There are 28 of these, but two are thought to be important for proton pump inhibition, CYS813 and CYS822. The need to achieve acid exposure in the parietal cell but not the stomach is why PPIs should be taken 20 min before breakfast.

These properties give PPIs their selectivity and potency and can explain potency differences between them. For example, rabeprazole as the most acid-labile PPI is the most potent, while the less reactive pantoprazole is the least potent[1–4] The mechanism of action based on covalent binding is similar to the way that aspirin works. Just as aspirin achieves permanent irreversible inhibition of platelet thromboxane synthesis to achieve an action that outlives its half-life, so too do PPIs. PPIs have quite a short pharmacological half-life (typically about 1 h), but this is largely irrelevant to their duration of activity, with synthesis of new pumps being required for restoration of acid secretion after approximately 24 h. Because PPIs do not work through receptor mechanisms, there is no pharmacological loss of activity by tachyphylaxis. However, long-term use can lead to a pseudo-tachyphylaxis in that parietal cell inhibition results in an increased parietal cell mass, which can be manifested as rebound hyperacidity on drug cessation.

All PPIs are eliminated by metabolism via the CYP2C19 pathway.[3] CYP3A4 also plays a role. Omeprazole and esomeprazole are not only metabolised by this pathway but they inhibit it also. This, as well as PH-dependent changes in absorption, gives rise to a number of drug interactions, the most important of which are listed in table 1. Inhibition is generally less or non-existent with other PPIs. Enantiomerically, pure esomeprazole is said to have a low dependency on CYP2C19 than racemate omeprazole and uses the CYP3A4 pathway to a greater extent. Because of its intrinsic instability, cytochrome P450 metabolism plays the least role in rabeprazole metabolism resulting in the lowest risk of drug interactions. Patients with mutant in CYP2C19 (poor metaboliser) experience increased effectiveness from all PPIs except rabeprazole.

Uses of PPIs

The main indications for PPI use are listed in box 1. Reflux remains the main one. Gastroenterologists will be familiar with the use of high-dose PPI intravenously for the prevention of re-bleeding following endotherapy for bleeding peptic ulcer.

Dyspepsia

Dyspepsia is a broad term that has probably changed its meaning over the course of history. PPIs are recommended for

Table 1 Interactions between proton pump inhibitors (PPIs) and other drugs*

Drug class	Drug	PPI	Effect on drug	Effect on PPI
Anticoagulants	Coumarins	Omeprazole, esomeprazole, pantoprazole	Probably enhanced effect	
Antiepileptic	Phenytoin	Omeprazole, esomeprazole	Enhanced effect	
Antibacterial	Clarithromycin	Omeprazole	Increased plasma level	Increased plasma level
Antifungal	Ketoconazole		Reduced absorption	
	Itraconazole		Reduced absorption	
Antiviral	Atazanavir	PPIs	Reduced plasma level	
	Nelfinavir	Omeprazole	Reduced plasma level	
	Raltegravir	Omeprazole	Increased plasma level	
	Saquinavir	Omeprazole	Increased plasma level	
	Tipranavir	Omeprazole and esomeprazole		Reduced plasma level
Antidepressant	Escitalopram	Omeprazole	Increased plasma level	
Vasodilator	Cilostazole	Omeprazole	Increased plasma level	
Antiplatelet	Clopidogrel	Omeprazole	Reduced activation	

*See text for description of interaction with clopidogrel.

Box 1 Uses of proton pump inhibitors

Pragmatic treatment of dyspepsia
Gastro-oesophageal reflux disease, including
- Management of upper airways complications*
- Diagnostic test*
- Prevention of strictures*
- Barrett's oesophagus and prevention of cancer*

Helicobacter pylori eradication
Peptic ulcer healing
Ulcer prophylaxis, principally in aspirin and non-steroidal anti-inflammatory drug users
Treatment of bleeding peptic ulcer
- Prevention of stress ulceration

Zollinger–Ellison syndrome
Reducing iron absorption in haemochromatosis*

*Unlicensed and/or unproven use

the pragmatic treatment of dyspepsia. While this is probably true for acid-like and reflux-like dyspepsia, their value in dysmotility-like dyspepsia has not been established.

Medical or surgical therapy of reflux?

This question has been subject to a Cochrane review.[5] PPIs are very effective treatment for reflux, but long-term use is necessary. The surgical alternative of laparoscopic fundoplication results in a quality of life that is similar to that of patients on PPIs, albeit with a number of adverse consequences such as dysphagia and an inability to belch and a need for supplemental PPI therapy in 36% of patients over 12 years.[6] The procedure has been analysed as cost-effective, but this merits a revisit in the light of the reduced cost of generic omeprazole and lansoprazole. In reality, the great majority of patients are managed medically, with laparoscopic fundoplication being reserved for a minority of patients who are drug averse or whose reflux is resistant to PPI therapy.

Upper gastrointestinal bleeding

High-dose PPI therapy (80 mg followed by 8 mg/h of omeprazole) is well established in the management of patients with ulcer bleeding and endoscopic stigmata,[7] and this role in the management of high-risk lesions has been confirmed in a large multinational randomised placebo controlled trial.[8] Furthermore, in certain populations, this strategy improves outcomes and increases cost-effectiveness of the overall treatment.[9] Their value prior to endoscopy in all comers has been much more difficult to establish. As long as 20 years ago, omeprazole was shown to be associated with an improvement in endoscopic signs, but did not show any effect on re-bleeding, surgery or death.[10] A more recent similarly designed trial, while being given a more positive interpretation by its authors, essentially showed the same results as the one previously conducted.[11] However, a Cochrane review of six relevant trials involving 2223 patients favours the former interpretation, that is, an improvement in the appearance of the bleeding lesion and a reduction in endoscopic intervention, but no impact on clinically meaningful end points.[12] Thus, while the notion of giving PPIs early in the presentation of unselected bleeders is appealing, there is no evidence to justify its adoption. Indeed a recent international consensus has supported endoscopic methods rather than pre-endoscopy PPIs as central to the achievement of haemostasis.[13]

Use of PPIs for patients on non-steroidal anti-inflammatory drugs

A wide range of studies have shown that PPIs are effective in preventing non-steroidal anti-inflammatory drug (NSAID)-associated endoscopic ulcers and ulcer bleeding.[14 15 16] In contrast to cyclo-oxygenase-2 (COX-2) inhibitors, no outcome studies have been performed to evaluate directly their ability to prevent NSAID-related ulcer complications in unselected populations, but indirect analyses suggest benefits.[14] Consequently, several meta-analyses have concluded that they are likely to be beneficial in this respect. As generic PPIs such as omeprazole have become cheaper, their use has become highly cost-effective for users of

both NSAIDs and COX-2 inhibitors. This has led the National Collaborating Centre for Chronic Conditions on behalf of the National Institute for Health and Clinical Excellence and the Royal College of Physicians to advise that all patients taking an NSAID or a COX-2 inhibitor should be given a PPI.[14] Indeed, in the highest risk patients, those who have already experienced a life-threatening gastric ulcer bleed, subsequent use of both a COX-2 inhibitor and a PPI was remarkably associated with no recurrent events at all.[17] In fact, fewer than a quarter of NSAID patients are on PPIs, and this is a prime example of an area where older messages are wrong, where pharmacy advisers should mount educational initiatives and where prescribers could make a major improvement in the safety of prescribing to their patients.[18]

Combination pills

VIMOVO is a novel combination of esomeprazole and naproxen and is likely to be launched in the UK during 2011.[19] The preparation uses non-enteric coated esomeprazole around enteric-coated naproxen. Impressively—and surprisingly, in view of the instability of PPIs in gastric acid[1]—a clinical trial has shown a reduction from 23% to 9% in the proportion of patients developing NSAID-associated gastric ulcers on VIMOVO compared with similar doses of naproxen alone.[10] Axorid is a preparation of ketoprofen and omeprazole, which is already available in the UK. Initially, it was rejected by the Scottish Medicine Consortium on economic grounds (although this decision was reversed following a resubmission by the manufacturers[20]). Similarly, when VIMOVO is launched, the issue will be whether the increased PPI adherence achieved by incorporation into a single pill justifies its price premium.

Use of PPIs in patients using aspirin

Some studies suggest that *Helicobacter pylori* eradication is sufficient to protect patients on aspirin from ulcer complications,[16] but the evidence is not good enough to be sure of this strategy. In patients taking aspirin, PPIs inhibit the development of ulcers and the recurrence of ulcer complications.[21 22] As with NSAIDs, PPI prophylaxis has been analysed as cost-effective in unselected patients on aspirin.[23] Such a precautionary approach is also wise given that some studies suggest cardiovascular disease may be a risk factor for ulcer complications.[24] As with NSAIDs, educational initiatives are needed to achieve an easy cost-effective improvement in the safety of aspirin prescribing. However, there may be problems in patients who also take clopidogrel.[25]

Do PPIs inhibit the effects of clopidogrel?

Clopidogrel is a pro-drug, requiring biotransformation via the CYP2C19 pathway to become active. PPIs, particularly omeprazole, are degraded through this pathway and can compete to reduce the activation of clopidogrel.[25] Whether these interactions are functionally or clinically significant remains controversial, but there are enough data for some conclusions to be drawn.

Using vasodilator-stimulated phosphoprotein as an index of platelet reactivity, several placebo controlled studies have shown that omeprazole reduces the response to clopidogrel, making a potential clinical interaction biologically plausible.[25] There are fewer data for other PPIs, but they appear to show less effect for pantoprazole.[26] A number of non-randomised descriptive clinical studies have shown that patients taking PPIs (principally the most widely used omeprazole) who are taking clopidogrel have an increased incidence of cardiovascular events.[27 28] In most of these studies, those on PPIs can be shown to or are likely to have higher cardiovascular risk factors, leading many authorities to conclude that the association arises through confounding.[29] Where groups are better balanced, the evidence for a clinical interaction diminishes sharply.[30–36] Moreover, in COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial, a large randomised controlled clinical trial comparing a clopidogrel/omeprazole combination pill with clopidogrel alone, there was no difference in the incidence of cardiovascular death and myocardial infarction between the two groups (HR for omeprazole 0.99, 95% CI 0.68 to 1.44).[37] By contrast, omeprazole significantly reduced gastrointestinal events (HR 0.34, 95% CI 0.18 to 0.63), suggesting substantial net benefit. This study was halted early due to sponsor bankruptcy, but this is unlikely to have influenced the results, beyond a relatively wide CI.

What should the prescriber do?

The COGENT study has not supported the hypothesis that omeprazole has a clinically significant effect on the activity of clopidogrel, while there was a clear-cut reduction in gastrointestinal events (figure 1). It seems that concerns over the effect of PPIs on clopidogrel may have been a storm in a teacup that should not detract from the recognition of their net benefit. Nevertheless, the COGENT study was not large enough to exclude anything less than a 44% increase in vascular end points with omeprazole. Where there are persisting concerns, pantoprazole 40 mg (the nearest bioequivalent to omeprazole 20 mg) could, on a theoretical and precautionary basis, be used instead.

Adverse effects of PPIs

In some ways, it was surprising how readily PPIs displaced H2 antagonists. Although their key feature was their greater efficacy, they are less effective in the short term for sporadic relief of dyspepsia because degradation by acid during the first few days of treatment makes them relatively ineffective during this time. In addition, they have a higher incidence of adverse effects, including headache, rash and diarrhoea (whether because of microscopic colitis, frank infection or by other mechanisms). However, recent data suggest that PPIs may have a more extended toxicity profile.

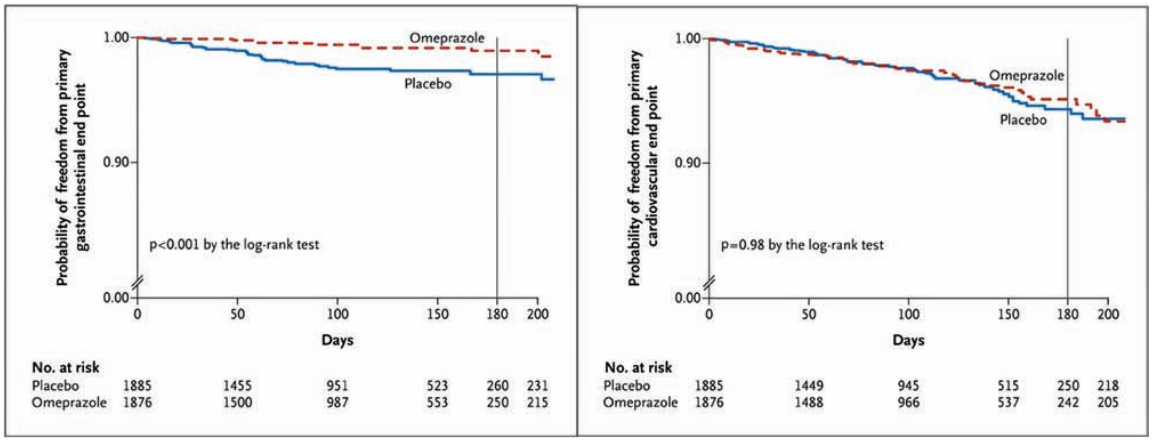

Figure 1 Clopidogrel and omeprazole. Reproduced with permission from Bhatt *et al*.[37]

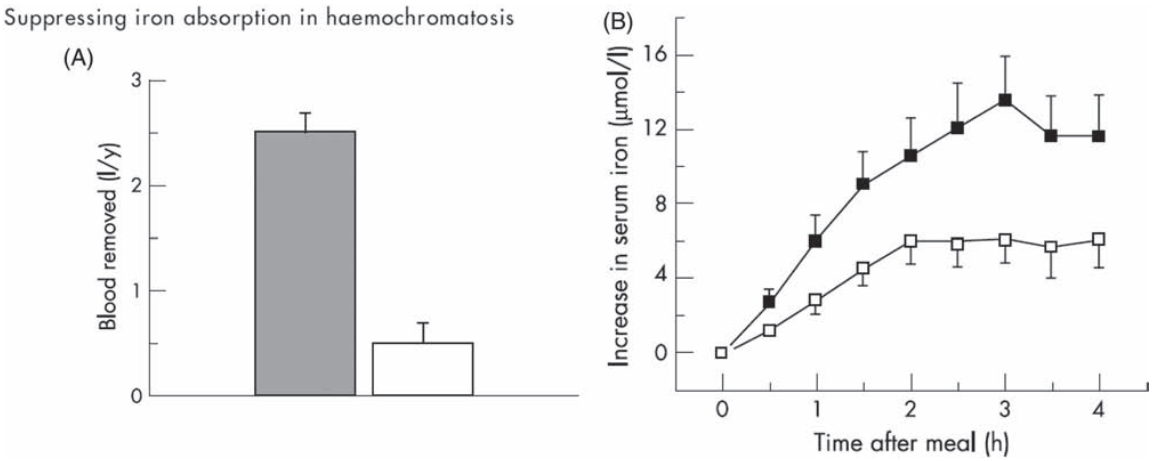

Figure 2 Influence of proton pump inhibitors (PPIs) on iron absorption. (A) Need for venesection in haemochromatosis patients before (closed bar) and during PPI therapy (open bar). (B) Reduced serum iron levels after an iron-containing meal off (closed points) and on a PPI (open points). Reproduced with permission from Hutchinson *et al*.[43]

Osteoporosis

Two epidemiological studies have identified an association between PPI prescription and the development of hip fracture and fractures overall. The adjusted OR for hip fracture ranges between 1.22 and 1.59[38] and between 1.1 and 1.4 for overall fracture risk.[39] What is not clear is whether this observed association is causal or consequential. In favour of a causal relationship, acid suppression has been shown to reduce the absorption of mineral calcium in the diet.[40 41] PPIs can also inhibit magnesium absorption, resulting in hypomagnesaemia menia, which may then impede magnesium-dependent secretion of parathormone and result in hypocalcaemia.[42] However, PPIs also inhibit osteoplastic activity thereby impeding bone absorption and therefore have a theoretical potential even to protect against osteoporosis. A non-causal relationship is also possible: patients in poorer general health and therefore more prone to osteoporosis may well have PPIs prescribed. This is at present an unresolved issue.

Iron deficiency

There are published case studies of iron malabsorption secondary to PPI use in iron-deficient people, probably due to the inability to oxidise iron from the ferrous to the absorbable ferric state (figure 2A). This is probably analogous to the situation in atrophic gastritis and loss of stomach acidity through infection with *H pylori* leading to iron deficiency. There is also evidence to suggest that PPIs can reduce the need for venesection in those with haemochromatosis[43] (figure 2B). There is, however, no evidence to suggest that even long-term use of PPIs can lead to an iron deficiency in an otherwise normal individual.

Vitamin B_{12} deficiency

Gastric acidity is necessary to activate pepsinogen to pepsin in order to release vitamin B_{12} from binding

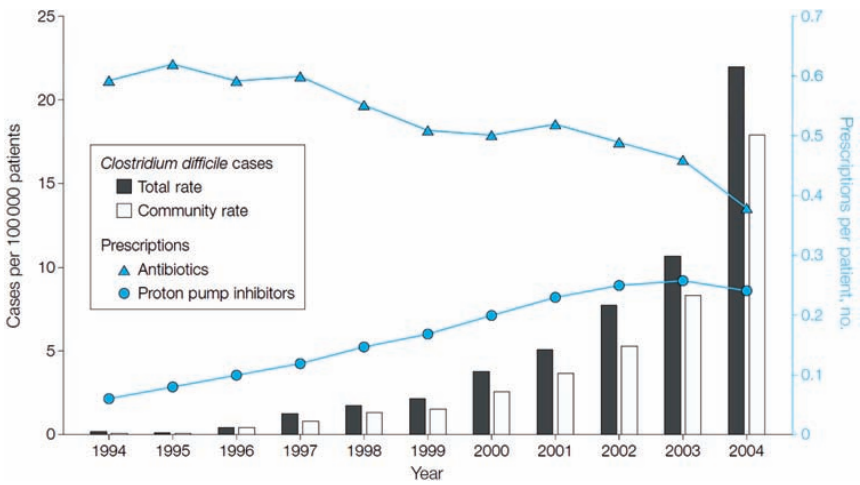

Figure 3 Rising *Clostridium difficile* infection rates despite falling antibiotic prescription but increasing proton pump inhibitor usage. Reproduced with permission from Dial *et al*.[51]

proteins. Acid suppression with therapeutic doses of PPI has been shown to reduce the absorption of vitamin B_{12}[44] and to lead to the food-cobalamin malabsorption syndrome.[45] With long-term use, there is a significant downward trend in vitamin B_{12} levels on those taking PPIs for 3 years or more.[46 47] In Zollinger–Ellison syndrome patients who require longer term high-dose PPI treatment, more profound reduction in B_{12} levels has been identified.[48] Monitoring would be wise in these individuals.

Cancer

Use of PPIs is associated with an increased incidence of gastric cancer.[49] The most prevalent view is that this arises by confounding rather than because PPIs cause cancer. Most cancers found in patients taking PPIs occur within 1 year of their commencement.

With longer term use, the possibility of a causal relationship cannot be entirely excluded, particularly since hypergastrinaemia and accelerated gastric atrophy could provide a mechanistic link. The possibility that long-term use of PPIs could increase the risk of gastric cancer cannot be dismissed, but a major effect seems unlikely on current evidence.

Enteric infections

Since the major physiological role of acid in the stomach is to sterilise food prior to delivery to the small intestine, it is to be expected that acid suppression will increase the risk of enteric infection. Early studies have shown an association between PPI use and *Salmonella* and *Campylobacter* infection.[50] Recently, a similar relationship has been found for *Clostridium difficile* infection and pseudomembranous colitis,[51 52] with *C difficile* infection rates rising in the face of declining antibiotic prescription but increasing use of PPIs (see figure 3). While there is debate about whether the relationship is causal or arises by confounding, it seems highly likely that it is a truly causal relationship. It has not been shown that acidic conditions found in the stomach reduce *C difficile* spore survival, but it has been postulated that the effect is on the bacilli in their vegetative state following germination in the stomach.

PPIs and eosinophilic oesophagitis

The increased recognition of eosinophilic oesophagitis in children and, to a growing extent, in adults has led to the recognition of a continuum between reflux oesophagitis through eosinophil-predominant oesophagitis to full-blown eosinophilic oesophagitis. Idiopathic eosinophilic oesophagitis is thought to arise by an allergic mechanism. It has been proposed that use of PPIs also leads to at least a *forme fruste* of the syndrome as a result of impaired initial digestion of food proteins secondary to acid inhibition and reduced pepsin activation,[53] but more research is needed.

Microscopic colitis

Although the formal evidence is relatively limited, most gastroenterologists clinically detect an association between PPIs, perhaps particularly lansoprazole, and microscopic colitis. A recent retrospective case-controlled study has suggested that PPI use was significantly higher in patients with collagenous colitis than in controls (38% vs 13%).[54]

Conclusion

Now that price has ceased to be an issue, the advantages and limitations of PPIs are easier to assess. Within the current landscape, they are grossly underused in patients taking aspirin or NSAIDs. Conversely, the recognition of new or potential adverse effects emphasises the fact that no drug comes medically cost free. But generic PPIs now come at an economic cost that is close to free, establishing a context that shows them to be widely underused. In particular, all patients taking NSAIDs or aspirin should be given a

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